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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,485	03/08/2001	Erin B. Dickerson	WARF-0003	4744

26259 7590 02/17/2004

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EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	09/801,485		DICKERSON ET AL.	
	Examiner		Art Unit	
	Jegatheesan Seharaseyon		1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to the amendment and remarks filed on 11/12/2003.

Claims 7-9 have been cancelled. Thus, claims 1-6 are pending.

2. Applicant's changing of the title is acknowledged.

Claim Rejections - 35 USC § 103, maintained

3. Claims 1-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U. S. Patent No. 5,994,104) in view of Ruoslahti et al. (U. S. Patent No. 6,180,084). Applicant's arguments filed on 11/12/2003 have been fully considered but are not persuasive.

Anderson et al. reference teaches the use of IL-12 fusion proteins for cancer therapy as indicated in Paper NO: 12. Although, the reference does not teach an IL-12 fusion protein operably linked to a RGD sequence, Anderson et al. does clearly teach IL-12 fusion protein with B7 (column 22-24), contrary to Applicant's assertion. Furthermore, it provides the motivation or suggestion for targeting rIL-12 to site of the tumor. It is stated that, "administration of rIL-12 has been shown to give the best therapeutic effects when delivered at the site of the tumor". Applicant further argues that Ruoslahti et al. do not remedy the deficiencies in the teachings of Anderson et al. Ruoslahti et al. reference was introduced to teach use RGD sequence to target α_v -integrins which are selectively expressed in the tumor blood vessels of patients (column 32, lines 54-57). In addition, it teaches the targeting of RGD conjugated doxorubicin to tumors (column 34, lines 63-67). Furthermore, it is stated that the administration to a tumor bearing mouse of a conjugate comprising a chemotherapeutic agent linked to a tumor homing molecule is more

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efficacious than administration of the agent, alone, in treating tumor (column 35 lines: 8-12). In the instant invention, IL-12 is the chemotherapeutic agent and RGD sequence is tumor homing molecule. Thus, providing the motivation or suggestion to combine the references.

Applicant also alleges that the prior art teachings of Lieschke et al., show that the activity of IL-12 is decreased in fusion proteins. Contrary to Applicants allegation, Lieschke et al. describe that the murine fusion protein IL-12.p40.L Δ (GlySer) linker was stably expressed (see abstract). In addition, Lieschke et al. further discloses that both murine and human IL-12 fusion proteins have comparable specific activity to that of native and recombinant IL-12 and retains antitumor activity *in vivo*. Thus, it is unclear how the art teaches away from forming IL-12 fusion proteins with antitumor activity.

In addition, Applicant also alleges that Reynolds et al. reference teaches that $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins are negative regulators of angiogenesis and that drugs targeting these receptors may act as agonists of angiogenesis as opposed to antagonists. Although, Reynolds et al. observe that $\beta 3$ -null or $\beta 3/\beta 5$ -null mice support tumor angiogenesis and tumor growth there is no suggestion that the integrin expression is affected or molecule containing the RGD sequence will not be able to bind to the intergrins in the absence of $\beta 3/\beta 5$ subunits. Since, Ruoslahti et al. teach the RGD sequence containing peptides binds to human αv -integrins, which are selectively expressed in the tumor blood vessels (column 32, lines 54-58), absent evidence to the contrary it is expected that RGD-IL12 fusion proteins will target tumor vasculature.

Therefore, it remains that it would have been obvious to one of ordinary skill in the art, at the time the invention was made to operably link interleukin-12 disclosed in Anderson et al. to a RGD-containing peptide protein described in Ruoslahti et al. to produce a fusion protein conjugate capable binding to α_V – integrins receptor on the surface of tumor blood vessels to destroy the blood vessels with greater efficacy and cause tumor necrosis with reasonable expectation of success, because Anderson et al. provides the motivation in that, rIL-12 has been demonstrated to have potent anti-tumor effects and have the best therapeutic effects when delivered at the site of tumor, in treating a tumor. Therefore, the instant invention is obvious over Anderson et al. (U.S. Patent No: 5,994,104) in view of Ruoslahti et al. (U.S. Patent No: 5,994,104).

4. No claims are allowable over prior art.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS

A handwritten signature in black ink, reading "Lorraine Spector". The signature is written in a cursive style with a large, looping initial "L".

**LORRAINE SPECTOR
PRIMARY EXAMINER**